UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

ID

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/135,238	08/17/98	NOLAN G	A-65635-1/DJ

HM22/1019

FLEHR HOHBACH TEST
ALBRITTON & HERBERT
4 EMBARCADERO CENTER SUITE 3400
SAN FRANCISCO CA 94111

EXAMINER	
SHUKLA,R	
ART UNIT	**PAPER NUMBER**
1632	19

DATE MAILED: 10/19/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary	Application No. 09/135,238	Applicant(s) NOLAN ET AL.	
	Examiner Ram R Shukla	Art Unit 1632	

-- Th MAILING DATE of this communication appears on the c ver sh et with the correspondenc address --

Period f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☐ Responsive to communication(s) filed on *30 September 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-17, 30, and 32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-17, 30, and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6,8,12* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

1. Applicant's election without traverse of the invention of group I (claims 1-17, 30 and 32) in Paper No. 9 is acknowledged.

2. Claims 18-29, 31, and 33-34 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 9.

3. Claims 18-29, 31, and 33-34 have been canceled as indicated in the Amendment filed 9-30-99 (paper #9).

4. Applicants claim to provisional application 60/066.063, filed 11-17-97 is acknowledged.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-17, 30 and 32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is referred to the revised interim guidelines on written description published December 21, 1999 in the Federal Register, Volume 64, Number 244, page 71427-71440 (also available at www.uspto.gov).

When the claims are analyzed in light of the specification, instant invention encompasses for nucleic acids that encode a TOSO protein that will hybridize to SEQ ID NO 1, or nucleic acids that have 70% sequence identity or that encode a protein that has 70% sequence identity or that have 70% sequence identity with the amino acids 18-253, 18-272, 273-390 of SEQ ID NO 2 or nucleic acids that have 70% identity with the nucleic acids encoding said proteins or fragments, vectors comprising said nucleic acids, host cells that comprise said vectors and processes for producing proteins encoded by said nucleic acids expressed in host cells. However, the specification discloses only Seq ID No 1 that encodes a polypeptide disclosed in SEQ ID NO 2. SEQ ID NO 3-21 also are amino acid sequences however, the

specification does not provide any disclosure as to what is their relationship to SEQ ID NO 2 or SEQ ID NO 1.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, Seq ID No 1 is the only species whose complete structure is disclosed. The specification does not provide any disclosure as to what would have been the sequence structure of all the claimed nucleic acids. Since the vectors and host cells comprise nucleic acids, the specification does not disclose what would be the structure of all the vectors and host cells comprising claimed polynucleotides. The specification also does not sufficient description as to how an artisan have practiced the methods of the claims 30 and 32, particularly when the specification does not provide sufficient description of the structure of the nucleic acids that are to be used in practicing the methods.

Next, then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence). In the instant case, the other identifying characteristic is the sequence identity and presence of certain motif or motifs. In regard to polynucleotides from species other than humans, it is noted that the specification does not provide any disclosure whether these sequences from other species would have had same characteristics would have had additional characteristics or properties. Since the claim recites only structure of the claimed polynucleotides, and does not recite any functional characteristics and the specification does not describe what functional assays would be used to identify the claimed nucleic acid molecules or what would be the function of the claimed nucleic acids, the written description requirement is not met.

This limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of cDNAs besides Seq ID No 1 that encode the amino acid sequences disclosed in Seq ID No 2, at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

7. Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a recombinant nucleic acid disclosed in SEQ ID NO 1 and which encodes the TOSO protein disclosed in SEQ ID NO 2, an expression vector comprising said recombinant nucleic acid, a host cell comprising the expression vector and a process of producing the TOSO protein of SEQ ID NO 2 by culturing said host cells and recovering the TOSO proteins from said host cells, does not reasonably provide enablement for other embodiments claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue".

The specification as filed is not enabling for claimed nucleic acids, vectors comprising said nucleic acids, host cells that comprise said vectors and processes for producing proteins encoded by said nucleic acids expressed in host cells, because the specification as filed does not provide sufficient guidance as to what would be considered a TOSO protein, whether the proteins with claimed sequence identity have TOSO function or biological activity, if not, how would an artisan have made and used them without undue experimentation.

First, what is a TOSO protein? Specification on page 10, lines 3-20, defines a TOSO a protein which states that if a protein has more than 50% sequence similarity or identity to SEQ ID NO 2, the protein is considered a TOSO protein. However, it is not clear how can only 50% or even 70% sequence similarity be the criteria for a protein to be a certain protein without any functional or other structural characteristics. For example, Sweet et al teach a protein called

PIGRL-1 which has 100% sequence similarity as well as identity with the amino acid sequence of SEQ ID NO 2 and it is associated with autoimmune disease (see sequence comparison with Sweet et al. Accession No X28178, N_Geneseq database, 3-31-1999). However, it is not clear this would be considered a TOSO protein. Likewise, Piskurich JF et al teaches a murine polymeric immunoglobulin receptor which shows 59.5% sequence similarity with the sequence of SEQ ID NO 2, again the specification does not provide any guidance whether this will this be considered a TOSO protein (see sequence comparison with Accession NO U06431, GenEmbl database, 5-26-1995).

Furthermore, the nucleic acid disclosed in Accession # AW402953 (EST database, 2-16-2000) shows 100 sequence identity and sequence similarity with the nucleic acid sequence encoding the amino acid sequence 41-141 of SEQ ID NO 2 and according it will hybridize with SEQ ID NO 1, again the specification does not provide any guidance whether this would be considered to encode a TOSO protein. The specification on page 10 and 11 also discloses that a protein fragment would be a TOSO protein if it had certain domain such as a transmembrane domain, cytoplasmic domain or extracellular domain, acidic amino acids, however, it is not clear whether a protein that has a cytoplasmic domain or extracellular domain which has 70% sequence similarity but no other sequence similarity would have TOSO activity, if not how would an artisan use such a nucleic acid or vector comprising said nucleic acid or host cell comprising said vector. For example, the nucleic acid disclosed in Accession No AI760373 would encode the amino acids 272-390 of SEQ ID NO 2, again it is not clear whether the protein would have the activity of a TOSO protein or whether the protein encoded by this nucleic acid would be considered a TOSO protein. The specification does not provide any guidance how would an artisan have used the nucleic acids, vectors or host cells comprising said vectors or nucleic acids or processes to make protein, where the nucleic acids have sequence similarity or identity as recited in certain domains of SEQ ID NO 2 but may not have the activity of TOSO protein.

Next, it is noted that a recombinant nucleic acid that encodes a TOSO protein whose amino acid sequence differs by only one amino acid would hybridize to SEQ ID NO 1, however, such a mutant protein may not have the activity of TOSO protein. The specification does not provide any guidance as to how an artisan would have used such a nucleic acid for the intended utility the function of such a protein was not known. It is recognized in the prior art that the

function of a protein depends on the sequence of its amino acids in a certain pattern, conformation of the protein due to the amino acid sequence, and the functional properties of the different parts of the protein (see second paragraph in Rudinger J in Peptide Hormones. Editor Parsons JA. Pages 1-7, 1976, University Park Press, Baltimore). Rudinger further add, "The significance of particular amino acids and sequences for different aspects of biological activity can not be predicted *a priori* but must be determined from case to case by painstaking experimental study" (see conclusion on page 6). The specification does not teach which changes in the amino acid sequences of the SEQ ID NO 2 would retain the function of the TOSO protein and therefore, the nucleic acids encoding such amino acid sequences could be used for the intended utilities. Particularly, if the amino acid sequence was changed by 30 percent, it is not clear whether the resultant protein will retain the function of the starting protein, if not how would the protein have been used for its intended utility. The specification does not teach how to use a nucleic acid that would have encoded a protein which was derived from the protein of SEQ ID NO 2 but did not have the function of the starting protein. Alternatively, the specification does not teach how would an artisan have made a polynucleotide that would have encoded a protein in which 30% amino acids would have been changed but the protein would have retained the function of the starting protein. As set forth in *In re Fisher,* 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

In conclusion, the specification as filed does not provide sufficient guidance, evidence, and working example, as to how an artisan of skill would have made and used the claimed invention commensurate in scope with claims and therefore, limiting the invention to a recombinant nucleic acid disclosed in SEQ ID NO and which encodes the TOSO protein disclosed in SEQ ID NO 2, an expression vector comprising said recombinant nucleic acid, a host cell comprising the expression vector and a process of producing the TOSO protein of SEQ

ID NO 2 by culturing said host cells and recovering the TOSO proteins from said host cells, is proper.

8. Claim 30 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of modulating apoptosis in an isolated mammalian T cells in vitro comprising administering to said isolated mammalian hematopoietic cell a recombinant expression vector wherein said recombinant expression vector expresses the TOSO protein disclosed in SEQ ID NO 2, does not reasonably provide enablement for a method of treatment of apoptosis related condition in a mammal and other claimed embodiments. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 32 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue".

The specification is not enabling for an in vivo method of modulating apoptosis in a cell by administering to said cell a nucleic acid encoding a TOSO protein or for a method of treatment of an apoptosis related condition in a mammal by administering to said cell a nucleic acid encoding a TOSO protein because, in addition to the issues raised and reasons set forth above in paragraph 7 in the enablement rejection of claims 1-17, neither the specification nor the prior art teaches as to whether a TOSO protein would have modulated apoptosis in any cell

in any mammal in vivo or would have treated any apoptosis related condition because the art of gene therapy and in vivo gene expression modulation is highly unpredictable and the specification as filed does not provide sufficient guidance, evidence and working examples for an artisan to have practiced the claimed method without undue experimentation.

First, the art of gene therapy using claimed polynucleotides in general is unpredictable as observed by several investigators and the specification does not provide suitable guidance as to how an artisan would have dealt with uncertainties and problems recognized in the art regarding the unpredictability of gene therapy in humans subjects.

Crystal (Crystal RG. Science 270:404-410.1995) assessed the state of the art of the gene therapy at the time the claimed invention was made. In the abstract, Crystal states "human gene therapy still faces significant hurdles before it becomes an established therapeutic strategy. " Later on page 409, he summarizes the problems faced in the art of gene therapy, such as inconsistent results, extrapolation of studies in mice to humans, production, and vector. He states " all of the human gene transfer studies have been plagues by inconsistent results, the bases of which are unclear" (see para 3 in col 1 on page 409). He also adds that there are several examples wherein prediction of gene transfer studies in experimental animals have not be borne out in human trials (see para 4 in col 1 on page 409). He also raises the issue of production of vectors, free of aggregation, contamination and variability from preparation to preparation, some of the problems that must be overcome before large clinical trials can be initiated. Additionally, there is the issue of an ideal vector? Crystal argues that an ideal vector for gene therapy is conceptually impractical because the human applications of gene transfer are broad and the ideal vector will likely be different for each application (see col 2 on page 409).

The report and recommendations of the panel to assess the NIH investment in research on gene therapy (Orkin SH and Motulsky AG. Report and Recommendations of the Panel to Assess the NIH investment in research on gene therapy, 1995) has also raised similar concerns. For example, the report states "while the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol, despite anecdotal claims of successful therapy and the initiation of more

than 100 recombinant DNA advisory committee (RAC) approved protocols." The committee further noted "significant problems remain in all basic concepts of gene therapy. Major difficulties at the basic level include shortcomings in all current gene transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host".

In a more recent assessment of the gene therapy art, Verma and Somia (Verma IM and Somia N. Nature 389: 239-242. 1997) summarize " In principle, gene therapy is simple: putting corrective genetic material into cells alleviates the symptoms of disease. In practice, considerable obstacles have emerged." They further add " But the problems- such as lack of efficient delivery systems, lack of sustained expression, and host immune response reactions- remain formidable challenges" (see the abstract). Although more than 200 clinical trials are currently underway worldwide, with hundreds of patients enrolled, there is no single outcome that we can point to as a success story" (see first and second paragraphs in col 1 on page 239).

Anderson (Anderson WF. Nature 392 (SUPP): 25-30, 1998) notes that since the approval of first clinical trial of gene therapy protocol in 1990, more than 300 protocols have been approved worldwide. He further adds, "The conclusions from these trials are that gene therapy has the potential for treating a broad array of human diseases and that the procedure appears to carry a very low risk of adverse reactions; the efficiency of gene transfer and expression in human patients is, however, still disappointingly low. Except for anecdotal reports of individual patients being helped, there is still no conclusive evidence that a gene therapy protocol has been successful in the treatment of a human disease."

Finally, Clay et al (Clark TM et al. Pathology Oncology Research 5:3-15, 1999) look at the some of the technical and biological hurdles that need to be addressed in gene therapy trials and conclude "Unfortunately, no gene therapy trial to date has been conclusively proven to be effective in treating the targeted disease.....It is clear that greater emphasis should be placed in vector development and understanding the biology of gene therapy targets if we expect gene therapy to be a viable option in the future..... Further advances will also be required in vector development and in establishing the optimum transduction conditions for target cells to enhance the efficiency of gene transfer and to provide prolonged gene expression."

In addition to the general issues of the art of gene therapy, there are specific issue related to the claimed TOSO protein related method. First, as noted in the specification, TOSO is expressed in T cell derived cell lines but not in other cells (lines 23-25, page 45), if so will TOSO modulate apoptosis in any and all cells, particularly when effect of TOSO is through T cell receptor dependent signal transduction (see figure 10). The specification does not provide any guidance as to whether TOSO would affect apoptosis in any and all cells in the absence of the signal transduction pathway wherein TOSO works. Next the specification does not provide any guidance whether the expression of TOSO would have been restricted to only those cells which are known to express TOSO cells or it would have been delivered to all the cells of the body. Furthermore, there is nothing on the record to teach whether expression of TOSO in cells where it is normally not expressed would have affected the normal physiology of the cells or would have induced apoptosis in normal cells. Additionally, the specification does not provide any guidance whether TOSO would have inhibited or activated apoptosis by tumor suppressor genes, such as P53 or bcl. Next, the specification does not provide any guidance as to whether TOSO would have been provided to a cell in vivo, would it have affected apoptosis.

It is noted that the prior art does not provide any guidance as to what would be the effect of TOSO on apoptosis in vivo. There is only one article published on TOSO which is by the applicants group and which describes cloning and characterization of TOSO (Hitoshi Y et al. Immunity 8: 461-471, 1998). In this article, inventors have disclosed that TOSO does not inhibit apoptosis by different mechanisms, such as staurosporine induced apoptosis or ceramide induced apoptosis. Additionally, TOSO did not have apoptotic effects downstream or at the level of capase-3. Likewise, TOSOS did not mediate BCL-XI or BCL-2 related apoptotic effects (see last paragraph in column on page 468). This indicates that TOSOS would not affect apoptotic effects of a cell where apoptosis was induced by different mechanism. Furthermore, Hitoshi et al note that TOSO may be responsible for down-regulating Fas-mediated apoptosis pathway of activated T cells, however, it is not clear as to when given how would TOSO discriminate between apoptosis of activated T cells that is normal versus apoptosis of activated T cells protein that may be disease related and needed therapeutic correction and the specification does not provide any guidance regarding this issue. Accordingly, the specification is not enabling for the claimed method of treatment by modulating apoptosis related conditions. In the absence of any guidance in the prior art on the role of TOSO in vivo, an artisan has to

depend on the teachings in the specification, however the specification does not provide sufficient guidance as to how an artisan would have addressed the issues of general nature and limitations of gene therapy methods as discussed above.

In conclusion, the specification as filed is not enabling for in vivo method of inhibiting apoptosis in any cells or a method of treatment of apoptosis related conditions and an artisan would have required undue experimentation to make and use the invention commensurate in scope with the claims and therefore, limiting the scope of the invention to a method of modulating apoptosis in an isolated mammalian T cells in vitro comprising administering to said isolated mammalian hematopoietic cell a recombinant expression vector wherein said recombinant expression vector expresses the TOSO protein disclosed in SEQ ID NO 2, is proper.

9. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached on (703) 305-6608. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 305-0196.

Ram R. Shukla, Ph.D.

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER